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Rom J Diabetes Nutr Metab Dis. **22**(2):175-185
doi: 10.1515/rjdnmd-2015-0022

PREVENTION OF CORONARY HEART DISEASE AND STROKE COMPLICATIONS IN TYPE 2 DIABETES MELLITUS: AN OBSERVATIONAL, PROSPECTIVE STUDY

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received: May 21, 2015 *accepted*: June 01, 2015
available online: June 15, 2015

Abstract

Background and Aims: *We assessed the effect of intensive therapy on modifiable cardiovascular (CV) risk factors and CV risk as compared to conventional therapy in patients with newly diagnosed type 2 diabetes mellitus (T2DM).* ***Material and Methods:*** *This was an observational, prospective study, conducted in Romania. During 1-year follow-up period the enrolled participants received either multi-factorial pharmacotherapy associated with intensive therapeutic education (Intensive group), or conventional therapy (Control group). Current analysis included data (anthropometric measurements, blood pressure and biochemical parameters) recorded at months (M) 0, 6 and 12. CV risk was calculated at M1 and M12 using the UK Prospective Diabetes Study Risk Engine.* ***Results:*** *138 patients aged 57.02±10.05 years were included in this analysis (69 in each group). At M6 and M12 a significant improvement of the majority of the modifiable risk factors in the Intensive group compared to the Control group was observed. At M12, coronary heart disease (CHD)/fatal-CHD risks were significantly lower in the Intensive (7.5%/3.1%) than in the Control (17.95%/10.3%) group ($p<0.05$). A similar trend was observed for the stroke/fatal-stroke risks.* ***Conclusions:*** *CHD/fatal-CHD and stroke/fatal-stroke risk burden decreased in newly diagnosed diabetic patients following multi-factorial pharmacotherapy association with intensive lifestyle changes during 1-year follow-up.*

key words: *type 2 diabetes, newly diagnosed patients, cardiovascular risk, lifestyle changes, multi-factorial therapy*

Background and Aims

Diabetes mellitus burden is increasing worldwide as a consequence of urbanization, lifestyle changes and population aging [1-3]. A systematic analysis including 370 country-years estimated that over 347 million persons worldwide are diagnosed with diabetes mellitus [4]. An estimation provided by the World Health Organization (WHO) suggests that by the year

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2030 diabetes will represent worldwide the 7th cause of death [5]. According to the International Diabetes Federation (IDF) data, in Romania in 2013 were reported 12,179 diabetes-related deaths in patients 20 to 79 years old [6].

Of all diabetic patients, approximately 90%–95% are diagnosed with type 2 diabetes (T2DM) [7,8]. T2DM is frequently associated with short-term and/or long-term complications, including microvascular complications (retinopathy, nephropathy and neuropathy), macrovascular complications (e.g. hypertension, myocardial infarction, stroke, coronary heart disease) and cancer [9-11]. Among complications, the cardiovascular diseases (CVD) represent one of the main cause of diabetes-related morbidity and mortality [8,12]. CVD risk and CVD-related mortality are 2–4-fold and 3-fold higher in patients with T2DM compared to non-diabetic subjects [12,13]. The observed increase in the CVD risk is the result of a complex interaction between multiple factors including obesity, dyslipidemia, hypertension, insulin resistance, physical activity [14-16].

The aim of our study was to assess the effect of intensive therapy on modifiable cardiovascular (CV) risk factors and CV risk as compared to conventional therapy in patients with newly diagnosed T2DM, during a 1-year follow up period, and to identify predictors related to CVD outcomes.

Materials and Methods

Participants and study design. This was an observational, prospective cohort study, which included data from 138 diabetic patients. The patients diagnosed and followed-up at "Regina Maria" Private Practice between January 2010 and January 2012 received multi-factorial pharmacotherapy associated with intensive lifestyle intervention (the standard of care in this clinic) represented the Intensive group. The data from patients receiving conventional therapy (Control group) were collected from a public hospital, County Emergency Hospital Bistrița-Năsăud, during the same time period.

The dataset from the Intensive group underwent a previous preliminary descriptive analysis designed to assess if multi-factorial pharmacotherapy associated with intensive lifestyle interventions impacts the modifiable CV risk factors, and CV risk in patients with newly-diagnosed T2DM [17]. Here we compared these data with a new dataset from a diabetic population which received only conventional therapy following T2DM diagnosis.

In both locations, the IDF 2009 criteria [18] were used for T2DM diagnosis. Among all the patients diagnosed with T2DM in these locations during the study period, there were included in the analysis only those meeting the following criteria: newly diagnosed with T2DM, age >30 years old, body mass index (BMI) ≥25 kg/m^2, if they gave their informed consent for inclusion in the study, and if confirmed their return for all planned study visits. The exclusion criteria were: diagnosis of other type of diabetes, ketoacidosis (diabetic complication), BMI <25 kg/m^2, chronic disorders in late stages, insulin therapy needed, and if they did not accept to be included in the study. Study procedures are detailed in Table 1.

The informed consent form was signed by all the participants included in the study before any study procedure and the protocol was approved by the ethical committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca and of the public hospital.

Anthropometric measurements included assessment of BMI (calculated by weight [kg]/height^2 [m] formula) and waist circumference (recorded by standard procedures).

Table 1. Study procedures.

Study visits (M)	Groups	
	Intensive group	Control group
1 (M0)	Anthropometric measurements Biochemical parameters, blood pressure Multi–factorial pharmacotherapy Lifestyle assessment Intensive therapeutic education CVD risk assessment	Anthropometric measurements Biochemical parameters, blood pressure Multi–factorial pharmacotherapy Lifestyle assessment Basic therapeutic education CVD risk assessment
2 (M1)*	Anthropometric measurements Biochemical parameters Blood pressure	–
3 (M3)*	Anthropometric measurements Biochemical parameters, blood pressure Intensive therapeutic education	–
4 (M6)	Anthropometric measurements Biochemical parameters, blood pressure Intensive therapeutic education	Anthropometric measurements Biochemical parameters, blood pressure
5 (M12)	Anthropometric measurements Biochemical parameters, blood pressure CVD risk assessment	Anthropometric measurements Biochemical parameters, blood pressure CVD risk assessment

*Results for these time points were published previously [17] and are not used in the current analysis. M, month; CVD cardiovascular disease.

Glycemia, glycated hemoglobin (HbA1c, immunoturbidimetric assay), total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) were measured by a fully automated analyzer (Cobas Integra 400 Plus, Roche). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation: [total cholesterol] minus [HDL-C] minus [TG]/5] if TG levels were <400 mg/dL . The Reaven score was calculated by TG/HDL formula. The therapeutic goal was met if the value of this parameter was <3 [19]. Blood pressure was recorded in sitting position by a standard mercury sphygmomanometer.

The multi-factorial pharmacotherapy targeted the glycemic, lipid and blood pressure control, according to the American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) recommendations at that time [20,21].

A questionnaire was filled up by each patient in order to assess lifestyle and plan accordingly the intensive therapeutic education provided to the Intensive group. Data regarding the age, gender, family history, diet habits, physical activity, smoking, social status, and any relevant information were recorded.

CVD risks were calculated by the UK Prospective Diabetes Study (UKPDS) model using the following variables: age, gender, ethnicity, smoking status, alcohol consumption, time from T2DM diagnosis, total cholesterol, HDL-C, systolic blood pressure and atrial fibrillation diagnosis [22]. Only patients with available results for all variables were included in the analyses. The UKPDS score classifies CVD (CHD and stroke) risk as follows [22]: decreased risk of CVD if the score is <15%, moderate risk of CVD if 15–30% and high risk of CVD if ≥30%: high risk of CVD.

Statistical analysis. Statistical analyses were done by the SPSS software for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). All statistical comparisons were made between the Intensive and Control groups. Demographic characteristic and multi-factorial treatment data were expressed as categorical data (percentages) or mean ± standard deviation (SD) and were compared between groups by Chi-Square Tests. Anthropometric and biochemical parameters, and CVD risk were expressed as mean ± SD deviation (SD) or median ± interquartile (Q1 and Q3) ranges. The means were compared by T-test and the medians by Independent Samples

Median test (non-parametric test). In order to compare the level of CVD risk reduction between groups, Delta risk was calculated by using the formula: calculated risk at 12 months minus calculated risk at month 0, and results were evaluated using the Independent Samples Mann-Whitney U Test. The Univariate General Linear Model was further performed to evaluate the delta risk adjusted for risk at month 0. Delta CVD risks were used as dependent variables and p was calculated using the Independent Samples Mann-Whitney U Test. A Multivariate Linear Regression Model was used to predict which of the risk factors have contributed to CVD risk change at month 12. CHD risk, logarithmic (log) fatal CHD risk, log stroke risk and log fatal stroke risk were used as dependent variables; ANOVA test was used for calculation and p was considered statistically significant if <0.05. The following factors were included in the analysis as predictors: group, gender, living area, BMI, waist circumference, TG, LDL and CVD at month 0. For all tests p-value was considered statistically significant if <0.05.

Results

Baseline characteristics. A total of 138 patients were enrolled and included in this analysis (69 in the Intensive group and 69 in the Control group). The mean age at diagnosis was 57.02 ± 10.05 (ranges 30 and 78) years. The baseline characteristics are presented in Table 2.

No significant difference between groups observed in terms of the prevalence of diabetic polyneuropathy (8 [11.6%] patients in the Intensive group and 9 [13.04%] patients in the Control group, p = 0.796) and retinopathy (2 [2.9%] and 4 [5.8%], p = 0.404).

Multi-factorial pharmacotherapy. The overall per group analysis of the multi-factorial pharmacotherapy showed significant changes in the percentages of participants receiving sulphonylureas, dipeptidyl peptidase 4 (DPP4) inhibitors, sartans, and calcium channel blockers medication in the intensive group compared to the control group during the 1 year follow-up as shown in Table 3.

Table 2. Demographic characteristics [n (%)] at baseline (month 0).

Category	Total N=138	Intensive group N=69	Control group N=69	p-value
Women	56 (40.6%)	17 (24.6%)	39 (56.5%)	**<0.001**
Medical history				
Cardiovascular disease	96 (69.6%)	39 (56.5%)	57 (82.6%)	**0.001**
Dyslipidemia	78 (56.5%)	43 (62.3%)	35 (50.7%)	0.170
Obesity	69 (50.0%)	43 (62.3%)	26 (37.7%)	**0.004**
Other*	51 (37.0%)	37 (53.6%)	14 (20.3%)	**0.029**
Self-monitoring	63 (45.7%)	50 (72.5%)	13 (18.8%)	**<0.001**
Family history				
Type 2 Diabetes	32 (23.2%)	16 (23.2%)	16 (23.2%)	1.000
Cardiovascular disease	38 (27.5%)	21 (30.4%)	17 (24.6%)	0.470
Obesity	38 (27.7%)	25 (36.8%)	13 (18.8%)	**0.019**
Urban area	66 (47.8%)	41 (59.4%)	25 (36.2%)	**0.006**
Education level				
Middle school graduate	12 (8.7%)	0 (0%)	12 (17.4%)	**<0.001**
High school graduate	75 (54.3%)	24 (34.8%)	51 (73.9%)	**<0.001**
College grad or higher	51 (40.0%)	45 (65.2%)	6 (8.7%)	**<0.001**
Smoking status at diabetes diagnosis				
Non-smoker	77 (55.8%)	31 (44.9%)	46 (66.7%)	**0.036**
Quit smoking for >6 moths	26 (18.8%)	16 (23.2%)	10 (14.5%)	**0.036**
Smoker	35 (25.4%)	22 (31.9%)	13 (18.8%)	**0.036**
Alcohol consumption	56 (40.6%)	30 (43.5%)	26 (37.7%)	0.488

*Health problems listed in patient's history (e.g. asthma, kidney disorders, hepatic disorders, pancreatitis, pancreatic abscess, gastritis, mammary cyst, ovarian cyst, glaucoma, etc.); N, maximum number of patients; n (%), number (percentage) of patients in a given category; The bolded values indicate a significant difference between groups.

Clinical and biochemical changes during the 1 year follow-up period. At baseline, all the variables were comparable between groups, except for the systolic blood pressure which was significantly higher in the Control group (Table 4). In both groups a decrease of all assessed variables was observed at month 6 and 12 compared to month 0, except for HDL-C were an increase was recorded (descriptive results). The month 6 and 12 statistical analysis showed that the improvement of all modifiable risk factors (except for BMI, TG and HDL-C at 6 months, respectively BMI at 12 months) was statistically significant higher in the Intensive group compared to the control group as shown in Table 4.

Table 3. Multi-factorial therapy during the 1-year follow-up period.

Category	Month 0				Month 6				Month 12			
	Total	Groups		p-value	Total	Groups		p-value	Total	Groups		p-value
		Intensive N=69	Control N=69			Intensive N=69	Control N=69			Intensive N=69	Control N=69	
Antidiabetic medication [n (%)]												
Biguanides	129	64 (49.6%)	65 (50.4%)	0.730	126	63 (50.0%)	63 (50.0%)	0.772	128	64 (50.0%)	64 (50.0%)	0.747
Sulphonylurea	39	18 (46.2%)	21 (53.8%)	0.571	34	9 (26.5%)	25 (73.5%)	**0.001**	34	9 (26.5%)	25 (73.5%)	**0.001**
DPP-4 inhibitors	7	7 (100%)	0 (0.0%)	**0.007**	16	15 (93.8%)	1 (6.3%)	**<0.001**	16	15 (93.8%)	1 (6.3%)	**<0.001**
GLP-1 agonists	0	0 (0.0%)	0 (0.0%)	NA	2	2 (100%)	0 (0.0%)	0.157	2	2 (100%)	0 (0.0%)	0.157
Lowering blood pressure medication [n (%)]												
Diuretics	40	14 (35.0%)	26 (65.0%)	**0.024**	-	13 (18.8%)	-	NA	36	11 (30.6%)	25 (69.4%)	**0.007**
ACE inhibitors	74	31 (41.9%)	43 (58.1%)	**0.032**	-	27 (39.1%)	-	NA	72	27 (37.5)	45 (62.5%)	**0.002**
Sartans (ARBs)	17	6 (35.3%)	11 (64.7%)	0.195	-	7 (10.1%)	-	NA	18	7 (38.9%)	11 (61.1%)	0.296
CCBs	31	14 (100%)	17 (54.8%)	0.541	-	14 (20.3%)	-	NA	37	10 (27.0%)	27 (73%)	**0.002**
Beta-blockers	50	22 (44.0%)	28 (56.0%)	0.288	-	24 (34.8%)	-	NA	50	21 (42.0%)	29 (58.0%)	0.191
Antiplatelet drugs	95	49 (51.6%)	46 (48.4%)	0.581	96	50 (52.1%)	46 (47.9%)	0.459	-	-	-	-
Dyslipidemia treatment [n (%)]												
Statin	99	49 (49.5%)	50 (50.5%)	0.850	105	52 (49.5%)	53 (50.5%)	0.721	-	-	-	-
Fibrates	39	28 (71.8%)	11 (28.2%)	**0.001**	36	22 (61.1%)	14 (38.9%)	0.133	-	-	-	-

Note: The bolded values indicate a significant difference between groups. N, maximum number of participants with available results; n (%), number (percentage) of participants in a given category; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide; ACE; angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; NA, not applicable; -, missing data.

At baseline no statistically significant difference was recorded between the Intensive and Control groups in terms of CHD (14.85% vs. 19%, respectively [p= 0.307]) and fatal CHD (6.85% vs. 11.45%, respectively [p= 0.089]) risks, while at month 12 the risks were significantly lower the Intensive group compared to the Control one (CHD: 7.5% vs. 17.95%, p= 0.026; fatal CHD: 3.1% vs. 10.3%, p < 0.001). The stroke related risks were significantly lower at baseline in the Intensive care group. To overcome this, we adjusted the calculated risk at 12 month for the baseline values. This allowed us to compare the risks and to exclude the false

lower values in the Intensive group. After adjustment for the baseline values the fatal CHD (Intensive group: 4.55 [2.73; 9.11], Control group: 7.53 [4.98; 12.95], p=0.049), stroke (Intensive group: 3.73 [1.80; 7.33], Control group: 6.49 [4.04; 11.53], p=0.003) and fatal stroke (Intensive group: 0.45 [0.21; 0.94], Control group: 0.86 [0.54; 1.78], p=0.005) risks at month 12 remained statistically significant lower in the Intensive care group than in the Control group. The difference between the CHD risk in the groups was no longer significant (Intensive group: 10.28 [7.25; 15.44], Control group: 12.70 [9.74; 19.27], p=0.35).

Table 4. Anthropometric and biochemical parameters [mean ± SD or median (Q1–Q3)] during the 1-year follow-up period.

Category	Month 0			Month 6			Month 12		
	Groups		p-value	Groups		p-value	Groups		p-value
	Intensive N=69	Control N=69		Intensive N=69	Control N=69		Intensive N=69	Control N=69	
BMI (kg/m^2)	31.95 (28.10; 35.30)	31.42 (28.45; 35.38)	0.609	28.90 (26.25; 32.22)	30.90 (28.10; 34.81)	0.173	29.40 (26.15; 32.05)	31.25 (28.06; 33.62)	0.200
WC (cm)	109.50 (102.00; 119.30)	108.00 (99.25; 116.75)	0.495	102.00 (98.00; 110.00)	108.00 (98.00; 115.00)	**0.006**	103.52 ± 10.39	107.23 ± 10.51	**0.039**
SBP (mmHg)	141.06 ± 18.22	151.13 ± 27.41	**0.012**	120.00 (110.00; 130.00)	140.00 (130.00; 160.00)	**<0.001**	126.39 ± 15.06	145.67 ± 23.40	**<0.001**
DBP (mmHg)	90.00 (80.00; 90.00)	90.00 (83.00; 91.75)	0.210	80.00 (80.00; 90.00)	80.00 (90.00; 90.00)	**0.036**	90.00 (80.00; 90.00)	90.00 (80.00; 90.00)	**<0.001**
Fasting Glycemia (mg/dl)	174.25 ± 45.32	172.43 ± 33.57	0.790	104.00 (98.00; 112.00)	110.00 (110.00; 130.00)	**0.022**	107.00 (98.00; 120.00)	117.00 (109.00; 134.00)	**0.049**
HbA1c (%)	8.11 ± 1.35	7.97 ± 1.03	0.487	6.00 (5.60; 6.40)	6.50 (6.20; 7.00)	**<0.001**	5.98 ± 0.64	6.59 ± 0.69	**<0.001**
Total-C (mg/dl)	224.00 (181.75; 244.00)	206.00 (192.00; 262.75)	0.173	160.27 ± 36.77	195.68 ± 40.42	**<0.001**	160.00 (133.50; 190.50)	195.00 (169.00; 216.25)	**0.005**
TG (mg/dl)	211.50 (127.00; 260.25)	177.50 (126.00; 238.00)	0.610	126.00 (92.85; 159.00)	147.50 (118.00; 187.75)	0.125	126.00 (89.5; 152.5)	154.5 (107.25; 209.75)	**0.008**
HDL-C (mg/dl)	40.00 (34.00; 46.25)	38.50 (34.00; 46.50)	0.389	46.65 ± 12.01	43.67 ± 8.67	0.097	49.17 ± 11.22	44.71 ± 9.32	**0.013**
LDL-C (mg/dl)	132.88 ± 40.27	142.99 ± 45.02	0.182	92.59 ± 33.83	116.09 ± 36.77	**<0.001**	94.78 ± 35.40	120.99 ± 35.49	**<0.001**
nonHDL-C (mg/dl)	176.00 (132.30; 199.25)	167.50 (149.25; 217.00)	0.733	113.29 ± 35.59	151.94 ± 42.99	**<0.001**	112.00 (88.50; 137.5)	148.00 (121.75; 173.50)	**<0.001**
TG/HDL-C	5.59 (3.15; 7.2)	4.70 (2.95; 6.89)	0.388	2.66 (1.84; 3.30)	3.46 (2.58; 4.79)	**0.006**	2.30 (1.64; 3.37)	3.62 (2.37; 4.99)	**0.003**

Note: The bolded values indicate a significant difference between groups. NA, not applicable; N, maximum number of participants with available results; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; Total C, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol.

The decrease in the risks (calculated by UKPDS Risk Engine estimated risk at month 12 minus risk at month 0) was significantly higher in the Intensive group compared to the Control group only for CHD (Intensive group: -9.9±9.9, Control group: -6.5±10.0, p=0.047). For fatal CHD (Intensive group: -3.2 [-8.10; -1.60], Control group: -3.15 [-8.15; -0.50]) and stroke (Intensive group: -0.30 [-1.10; 0.0], Control group: 0.10 [-1.10; 1.00] risks, although the decrease in the calculated risks was higher in the Intensive group than in the Control group, it did not reach statistical significance. Similar decreases in the fatal stoke risks were observed in both groups (Intensive group: -0.10 [-0.30; 0.0], Control group: -0.10 [-0.40, 0.20], p=0.674). The following predictors (value ± standard error) were identified after the Multivariate Linear Regression analysis: for log CHD at 12 months: the study group, LDL-C at month 0 and CHD risk at month 0; for log fatal CHD, the study group and fatal CHD risk at month 0; for log stroke: the study group and stroke risk at month 0; and for log fatal stroke: the study group and the fatal stroke risk at month 0.

Discussions

The present study was carried out to assess the estimated CHD/fatal CHD and stroke/fatal stroke risks changes during 1 year after T2DM diagnosis and to identify the predictors responsible for the CVD outcomes in a diabetic population from Romania. In the current study, we showed that the association of multi-pharmacotherapy with intensive lifestyle interventions during 1-year follow-up period determined a significant reduction (with approximately 50%) of CHD/fatal CHD and stroke/fatal stroke risks in patients newly diagnosed with T2DM. As compared to the Control group, the intensive lifestyle interventions determined a significantly higher reduction of the estimated CHD risk at 12 months, and non-significant reductions of fatal CHD and stroke risks.

Up to date, multiple interventional studies were conducted in order to assess the effect of interventions targeting the modifiable CVD risk factors on the CVD-related morbidity and mortality. In a study conducted in USA Nathan Wong et al. showed that an intensive control of the CV risk factors in patients with T2DM could reduce with approximately 55% the CHD events over 10 years (ranges: 35% and 61%, depending on the type of control applied to the modifiable risk factors) [23]. Similar results were published by the investigators of Steno-2 study in which was shown that intensive therapy targeting HbA1c, LDL Cholesterol and blood pressure led to a 59% reduction in the relative risk after a mean follow-up of 13.3 years [24]. Another study conducted in China showed that the strict control of CV risk factors (HbA1c, blood pressure or LDL-C) over 5.7 years follow-up period was associated with a 31% reduction of CHD events [25].

Nonetheless, negative results have also been communicated. Thus, the United Kingdom Prospective Diabetes Study (UKPDS), the first designed to assess the effects on intensive glycemic control on the CVD risk in patients with newly diagnosed T2DM, showed a significant decrease only for microvascular complications (21%), with no effect on CVDs incidence (myocardial infarction risk was non-significantly reduced, with only 16% in the sulphonylurea/insulin intensively treated patients) [26,27]. The Look AHEAD (Action for Health in Diabetes) study evaluated if behavioral interventions targeting weight loss in overweight and obese patients with T2DM could improve long-term CVD-related mortality and morbidity [28]. After 9.6 years of follow-up, even if weight significantly decreased and an improvement of

CVD risk factors (except for low-density lipoprotein cholesterol [LDL-C]) was recorded in patients with intensive behavioral intervention, the non-fatal myocardial infarction and stroke, and CVD-related mortality were not significantly decreased compared to the control group [28].

As these negative results came from landmark trials, different hypotheses aiming to find an explanation have been issued. For UKPDS, one of the explanations was the enrollment of patients with target organ damage, including cardiovascular complication [29]. Additionally, even if the glycemic control was strict, the benefits were notable only following several years of therapy, compared to the results observed for the intensive blood pressure control; these suggest that intensive glycemic control alone is not suitable for all patients, especially for elderly if it is not associated with other drugs targeting the CV risk factors reduction (e.g. aspirin, lipid lowering drugs or antioxidants) [30]. This hypothesis was further confirmed by the ACCORD trial, in which it was showed that intensive hypoglycemic therapy aiming to achieve normal glycated hemoglobin levels was associated with increased mortality and no effects on the major cardiovascular events [31].

Regarding the variables used in the risk calculations, we observed significantly lower HbA1c, total cholesterol and HDL-cholesterol values at 12 months in the Intensive group compared to the Control group; at baseline these variables were similar in the two groups. For the smoking, we could not evaluate the status at 12 months, as it was only recorded at baseline. In terms of systolic blood pressure, an interesting finding was the lower values in the Intensive group compared to the Control at 12 months, although a higher percentage of patients in the Control group were using antihypertensive drugs. Furthermore, the decrease was higher in the Intensive group compared to the Control: -14.67 mmHg vs. -5.46 mmHg. Although epidemiological studies showed that blood pressure is positively associated with BMI values and changes [32-35], in our study the lower values of systolic blood pressure at 12 months in the Intensive group cannot be explained by the differences in BMI values which were similar in the two groups. Another factor which has been shown to be involved in the association of blood pressure and obesity is the body fat distribution [36,37]; in particular visceral fat accumulation which has been shown to be associated with hypertension [36-38]. The Olivetti Prospective Heart Study, enrolling 1079 men, of which 768 without pharmacological treatment for hypertension, showed that visceral accumulation of body fat was associated with increased blood pressure, and this association was independent of BMI [38]. Similar to these observations, in our study we observed that at 12 months waist circumference was significantly lower in the Intensive group compared to the Control group.

In our study we have shown that the reduction of estimated CV risk can be achieved after only 1 year of intervention and this type of intervention is feasible in the daily practice for both physicians and patients. However, it should be noted that due to short follow-up we did not assess the impact of the intensive multifactorial intervention on the actual incidence of CVD and mortality, this representing a limitation of this study.

Regarding the modifiable risk factors, in our study the early intensive behavioral approach and multifactorial pharmacotherapy led to the achievement of the target optimal goals recommended by ADA at the time of patient treatment [39-41], including systolic blood pressure, LDL-C, TG, HDL-C and TG/HDL-C.

Similar results were reported by studies assessing early lifestyle interventions in patients newly diagnosed with T2DM [24,42,43]. In the control group, the optimal goals were not met. Our results suggest that the strict control of all modifiable risk factors shortly after the diagnosis of T2DM could prevent approximately 50% of the CHD and stroke events in patients that follow an intensive therapy for diabetes management.

Our study has limitations. The most important one is the short-term follow-up which did not allow us to evaluate the effect of multifactorial intervention on the CV morbidity and mortality. However the inclusion of real life patients' data will allow us to continue the follow-up without any budget restrictions. Another limitation was that most of the baseline characteristics of the participants included in the analysis were not comparable between groups at baseline. This limitation can occur in observational studies because of the limited population size within the defined time frame.

Conclusions

We showed that multi-factorial pharmacotherapy associated with intensive lifestyle changes (dietary habits, physical activity and patient continuous education) is associated with a decrease in estimated CHD/fatal CHD and stroke/fatal stroke risk burden. Furthermore, we showed that this type of intervention is feasible in daily practice, not only in clinical trials, without posing any burden on the physicians or patients. Hopefully our study will motivate clinicians to follow this approach in order to control the modifiable factors that may allow to reduce the incidence of CHD and stroke events, and to improve the quality of life of each patient.

REFERENCES

1. **Chen L, Magliano DJ, Zimmet PZ.** The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. *Nat Rev Endocrinol* 8: 228–236, 2011.

2. **Sapkota S, Brien JA, Greenfield J, Aslani P.** A systematic review of interventions addressing adherence to anti-diabetic medications in patients with type 2 Diabetes—impact on adherence. *PLoS One* 10: e0118296, 2015.

3. **Ginter E, Simko V.** Type 2 diabetes mellitus, pandemic in 21st century. *Adv Exp Med Biol* 771: 42-50, 2012.

4. **Danaei G, Finucane MM, Lu Y et al.** National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 378(9785): 31–40, 2011.

5. **World Health Organization.** Global status report on non-communicable diseases 2010: World Health Organization; 2011. Available from: http://www.who.int/nmh/publications/ncd_report2010/en/.

6. **International Diabetes Federation.** International Diabetes Federation Atlas, Sixth edition, 2013. Available from: http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf.

7. **Tripathi BK, Srivastava AK.** Diabetes mellitus: complications and therapeutics. *Med Sci Monit* 12: RA130–RA147, 2006.

8. **Wu Y, Ding Y, Tanaka Y, Zhang W.** Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci* 11: 1185–1200, 2014.

9. **Zhao Y, Jiang Z, Guo C.** New hope for type 2 diabetics: targeting insulin resistance through the immune modulation of stem cells. *Autoimmun Rev* 11: 137–142, 2011.

10. **Mahajan A, Sharma S, Dhar MK, Bamezai RNK.** Risk factors of type 2 diabetes in population of Jammu and Kashmir, India. *J Biomed Res* 27: 372–379, 2013.

11. **Bianchi C, Del Prato S**. Metabolic memory and individual treatment aims in type 2 diabetes – outcome-

lessons learned from large clinical trials. *Rev Diabet Stud* 8: 432–440, 2011.

12. Joseph JJ, Donner TW. Long-term insulin glargine therapy in type 2 diabetes mellitus: a focus on cardiovascular outcomes. *Vasc Health Risk Manag* 11: 107–116, 2015.

13. Taylor KS, Heneghan CJ, Farmer AJ et al. All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large UK primary care database. *Diabetes Care* 36: 2366–2371, 2013.

14. del Cañizo-Gómez FJ, Moreira-Andrés MN. Strict control of modifiable cardiovascular risk factors in patients with type 2 diabetes mellitus. *Med Clin (Barc)* 130: 641–644, 2008.

15. Fonseca VA. Risk factors for coronary heart disease in diabetes. *Ann Intern Med* 133: 154–156, 2000.

16. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes* 5: 444–470, 2014.

17. Ştefan RM, Niţă C, Crăciun A, Rusu A, Hâncu N. Effect of the early intensive multifactorial therapy on the cardiovascular risk in patients with newly diagnosed type 2 diabetes: an observational, prospective study. *Clujul Medical* 88: 168–174, 2015.

18. International Diabetes Federation. IDF Diabetes Atlas 4th Edition, International Diabetes Federation, 2009. Available from: www.diabetesatlas.org.

19. Rydén L, Standl E, Bartnik M et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 28: 88–136, 2007.

20. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. *Diabetologia* 52: 17–30, 2009.

21. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35: 1364–1379, 2012.

22. Risk calculator UKPDS. Available from: integrate.ccretherapeutics.org.au/Calculator/UkPds.aspx.

23. Wong ND, Patao C, Malik S, Iloeje U. Preventable coronary heart disease events from control of cardiovascular risk factors in US adults with diabetes (projections from utilizing the UKPDS Risk Engine). *Am J Cardiol* 113: 1356–1361, 2014.

24. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 358: 580–591, 2008.

25. Kong APS, Yang X, Ko GTC et al. Effects of treatment targets on subsequent cardiovascular events in Chinese patients with type 2 diabetes. *Diabetes Care* 30: 953–959, 2007.

26. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352(9131): 854–865, 1998.

27. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321(7258): 405–412, 2000.

28. The Look AHEAD Research Group, Wing RR, Bolin P et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 369: 145–154, 2013.

29. Robertson KE, Prince MJ. What the UKPDS really says about cardiovascular disease and glycemic control. *Clinical Diabetes* 17: 109–110, 1999.

30. King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacology* 48: 643–648, 1999.

31. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358: 2545–2559, 2008.

32. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 240: 1607–1610, 1978.

33. MacMahon S, Cutler J, Brittain E, Higgins M. Obesity and hypertension: epidemiological and clinical issues. *Eur Heart J* 8(Suppl B): 57–70, 1978.

34. Cassano PA, Segal MR, Vokonas PS, Weiss ST. Body fat distribution, blood pressure, and hypertension. A prospective cohort study of men in the Normative Aging Study. *Ann Epidemiol* 1: 33–48, 1990.

35. Drøyvold WB, Midthjell K, Nilsen TI, Holmen J. Change in body mass index and its impact on blood pressure: a prospective population study. *Int J Obes (Lond)* 29: 650–655, 2005.

36. Johnson D, Prud'homme D, Despres JP, Nadeau A, Tremblay A, Bouchard C. Relation of abdominal obesity to hyperinsulinemia and high blood pressure in men. *Int J Obes Relat Metab Disord* 16: 881–890, 1992.

37. Okosun IS, Prewitt TE, Cooper RS. Abdominal obesity in the United States: prevalence and attributable risk of hypertension. *J Hum Hypertens* 13: 425–430, 1999.

38. Siani A, Cappuccio FP, Barba G et al. The relationship of waist circumference to blood pressure: the Olivetti Heart Study. *Am J Hypertens* 15: 780–786, 2002.

39. American Diabetes Association. Standards of medical care in diabetes – 2009. *Diabetes Care* 32[Suppl 1]: S13–S61, 2009.

40. American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care* 32[Suppl 1]: S11–S6, 2010.

41. American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care* 35[Suppl 1]: S11–S63, 2012.

42. Florea M, Niţă C, Florea R, Hâncu N. Cardio-metabolic risk factors control in newly diagnosed type 2 diabetic subjects. *Rom J Diabetes Nutr Metab Dis* 20: 279–286, 2013.

43. Andrews RC, Cooper AR, Montgomery AA et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. *Lancet* 378: 129–139, 2011.